Inhibition of the chlorinating activity of myeloperoxidase by tempol

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Despite of the therapeutic potential of tempol and related nitroxides as antioxidants, their effects on myeloperoxidase (MPO)-mediated processes remain little investigated. Recently, we determined the second order rate constant value of the reaction of tempol with MPO-I and MPO-II (3.8×10^6 and 2.1×10^4 M^{-1} s^{-1}, respectively). Also, we showed that tempol efficiently inhibits MPO-mediated nitrations because of its rapid reaction with nitrogen dioxide radical to produce the oxammonium cation, which recycles back to tempol by reaction with hydrogen peroxide. Since MPO-mediated chlorinations do not depend on radicals, it became interesting to examine tempol effects on them. Here, we show that tempol (1-10 μM) inhibits hypochlorous acid formation and hydrogen peroxide consumption in incubations containing 5 U/ml MPO, 100 mM chloride, 0.1 mM DTPA and 15 mM taurine. The behavior of tempol differed from that of a similarly good MPO substrate, such as tyrosine, but was similar to that of indole compounds, which react rapidly with MPO-I but not with MPO-II. Several lines of evidence indicate that indole-derivatives bind to MPO, but a favorable binding of tempol to the hydrophobic cavity of MPO has yet to be demonstrated. To this end, the inhibitory effects of tempol derivatives containing aromatic structures on MPO chlorinating activity are being investigating. In parallel, these nitroxides are being docked into the active site of MPO. The inhibition of MPO chlorinating activity by nitroxides is yet another mechanism to explain their potent antioxidant properties in animal models of inflammation.